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Contractor	HASKELL LABORATORY		
Document Title	INITIAL SUBMISSION: STUDY OF PRIMARY SKIN IRRITATION AND SENSITIZATION OF 4(4-ISOCYANATOBENZYL METHYL) CYCLOHEXYL ISOCYANATE, * IN GUINEA PIGS WITH COVER LETTER DATED 10/15/92		
Chemical Category	4(4-ISOCYANATOBENZYL METHYL)CYCLOHEXYL ISOCYANATE;		

8(e)

CAP

(COMPLIANCE AUDIT PROGRAM)

11768

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Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91 CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide" states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
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Legal D-7158
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INIT 89/83/92



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ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation's TSCA §8(e) reporting standard². This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.³ Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

²In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment. See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

³A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteria. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- o the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵
- o the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- o the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

⁴The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

⁵ See, e.g., 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). See also, Rollins Environmental Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

"a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified. See, 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy", 43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide*.

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specific effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical. Unknown effects occurring during such a range test may have to be reported if they are those of concern to the Agency and if the information meets the criteria set forth in Parts V and VII."

⁷Guide at pp.22, 29-31.

⁸Guide at pp-34-36.

⁹Guide at pp-34-36.

¹⁰Guide at pp-34-36.

¹¹Guide at pp-22; 36-37.

¹²Guide at pp-22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp-22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y ¹⁸	Y ¹⁹
<i>In Vivo</i>	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y} ²⁰	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reproductive	N	N

¹⁵Guide at pp-23; 33-34.

¹⁶43 Fed Reg at 11112
"Cancer" listed

¹⁷Guide at pp-21.

¹⁸43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

CAS # 584-34-9; 5124-30-1

**Chem: 4(4-Isocyanatobenzyl methyl)cyclohexyl isocyanate;
2,4-toluene diisocyanate; methylene-bis-(4-cyclohexyl-
isocyanate)**

**Title: Primary skin irritation and sensitization tests on
guinea pigs**

Date: 2/5/70

Summary of effects: Sensitization

Copies to: P. R. Johnson (6)

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 66-70

MR NO. 815

Materials Tested:

4(4-Isocyanatobenzylmethyl) Cyclohexyl Isocyanate (> 90% active ingredient)
2,4-Toluene Diisocyanate
Methylene-bis (4-cyclohexylisocyanate) (99.49% active ingredient)

Haskell Nos.

5273

4954

4679

Other Codes

PIBC; Sample of C. F. Irwin

TDI; "Hylene" T; LR4-200

PICM-20; ECD-390 LR-12-414;
Lot No. 4

Materials Submitted by: P. R. Johnson, Elastomer Chemicals Department
Experimental Station

PRIMARY SKIN IRRITATION AND SENSITIZATION TESTS ON GUINEA PIGS

Procedure: Solutions of each material in f.a.d.* were tested by topical application on two groups of ten male albino guinea pigs.

Test Group I: In the test for primary irritation, applications of one drop (ca. 0.05 ml) each of 1% and 0.1% solutions were lightly rubbed into intact shaved skin. A series of exposures was given to the animals over a three-week period to determine the sensitization potential. The test material was applied to the clipped abraded skin of five animals as solutions in f.a.d. in a series of nine applications. A 1% solution was used except for the second treatment which was given at 2%. The remaining five animals were given four intradermal injections (0.1 ml each of 1% solution in dimethyl phthalate). A two-week rest period was followed by a challenge test (I) consisting of applications of 1% and 0.5% solutions on both intact and abraded skin. A group of previously unexposed animals (controls) was similarly tested. Thirteen days after the first challenge test, a second test (II) consisting of challenge and cross-challenge tests was done with 1% PIBC, 1% TDI, and 0.1% PICM-20 (all solutions were in f.a.d.) on intact skin.

Test Group II: In the test for primary irritation, applications of one drop (ca. 0.05 ml) each of 100% (undiluted product), 50%, 5%, and 2% were lightly rubbed into intact shaved skin. A four-week rest period was followed by a challenge test (Ia) consisting of applications of 1% and 0.5% solutions on both intact and abraded skin. Fifteen days after the first challenge test, a second test (IIa) consisting of challenge and cross-challenge tests was done with 1% PIBC, 1% TDI, and 0.1% PICM-20 (all solutions were in f.a.d.) on intact skin.

* f.a.d. = 13% (w/v) solution of guinea pig fat in a 1:1 (v/v) acetone-dioxane mixture.

Results:

Primary Irritation with H-5273							
Animals	Concentration	Reactions ^{a)} on Intact Skin				Reactions ^{a)} on Abraded Skin	
		1 Day	2 Days	3 Days	7 Days	1 Day	2 Days
Test Group I	1%	8+, 2 negative	8+, 2 neg.	—	—	—	—
	0.1%	2+, 8 negative	10 negative	—	—	—	—
Test Group II	100% (undiluted)	++++ (5/5)	++++ (5/5)	++++ (5/5)	++++ (5/5)	—	—
	50%	++++ (5/5)	++++ (5/5)	++++ (5/5)	++++ (5/5)	—	—
	5%	10++++	10++++	10++++	10++++	—	—
	2%	3++++, 6++, 1+	8++++, 2+	8++++, 2+	4+, 6 neg.	—	—
Controls	1%	10+	9+, 1 neg.	—	—	10+	10+
	0.5%	7+, 3 negative	3+, 7 neg.	—	—	6+, 4 neg.	2+, 8 neg.

NOTE: All 100% and 50% application sites and occasionally the 5% application site had a rough leathery texture to the skin from one to seven days. Some slight to moderate desquamation was seen at seven days at the 100% and 50% application sites. Readings were also made at 16 days and at this time were all negative with some skin tinting** at the 100%, 50%, and 5% application sites.

a) Reaction code: +, ++, +++ = Mild, moderate, strong erythema; ++++ = erythema with edema; +++++ = necrosis; neg. = negative.

** The skin showed no erythema, but did show tinting (brown to almost colorless) at the treated site.

Results: (Cont'd.)

Challenge and Cross-Challenge Reactions							
Test	Haskell No.	Conc.	Reactions ^{a)} on Intact Skin		Reactions ^{a)} on Abraded Skin		No. of Guinea Pigs Sensitized
			1 Day	2 Days	1 Day	2 Days	
I Test Group I	5273	1%	3++++, 3+++, 4++	4++++, 6+	3++++, 3++, 4+	3++, 7+	6/10
		0.5%	1+++, 6++, 3+	2++, 8+	4++, 6+	8+, 2 negative	
II Test Group I	5273	1%	1++++, 6+++, 2++, 1+	3+++, 4++, 3+	—	—	7/10
	4954	1%	3++, 7+	6+, 4 negative	—	—	0/10
	4679	0.1%	3++, 6+, 1 negative	5+, 5 negative	—	—	0/10
Ia Test Group II	5273	1%	8++++, 1+++, 1++	8++++, 1++, 1+	5++++, 1+++, 4++	4++++, 1++, 5+	9/10
		0.5%	6++++, 3+++, 1++	5++++, 1+++, 2++, 2+	2++++, 3+++, 5++	2++++, 4++, 4+	
IIa Test Group II	5273	1%	1++++, 8++++, 1+	1++++, 8++++, 1+	—	—	9/10
	4954	1%	1++, 9+	1++, 7+, 2 neg.	—	—	0/10
	4679	0.1%	1++++, 9+	1+++, 9+	—	—	1/10

Summary: 4(4-Isocyanatobenzylmethyl) cyclohexyl isocyanate (PIBC) as the undiluted product and as 50% and 5% solutions in fat-acetone-dioxane was strongly irritating to guinea pig skin through seven days. The 2% solution produced variable strong to mild reactions while the 1%, 0.5%, and 0.1% solutions produced mild to no irritation.

Sensitization occurred in six out of ten to nine out of ten animals tested in the two groups. A greater number of sensitization reactions occurred in the group exposed to the higher concentrations (undiluted or 50% and 5% and 2%) for primary irritation than occurred in the group given lower concentrations for primary irritation and subsequent sensitizing treatments. When the test animals were tested for cross-sensitization with 2,4-toluene diisocyanate (TDI) and methylene-bis (4-cyclohexylisocyanate) (PICM-20), it was found that only one animal out of the twenty tested had positive reactions to PICM-20. This indication of possible cross-sensitization between PIBC and PICM-20 suggests that an individual sensitized to one isocyanate should avoid another isocyanate. This suggested cross-sensitization might be confirmed by a special animal experiment.

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Summary: (Cont'd.)

PIBC is a strong skin irritant and a strong sensitizer of guinea pig skin. Similar results were obtained with PICH-20 (unreported Haskell Laboratory data N.B. 712-40) and 4-(cyclohexylmethyl), cyclohexyl isocyanate (DDC) (Haskell Report No. 67-70). TDI is also a strong sensitizer, but appears not to be so irritating as PIBC, DDC, and PICH-20 (MR 13-173 and other unreported Haskell projects).

Report by:

Karen M. Frank
Karen M. Frank

Date:

February 5, 1970

Report No. 65-70

N.B. 712-130.

Approved by:

Gordon J. Stopps
Gordon J. Stopps
Assistant Director

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